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(21) International Application Number: PCT/EP96/01769 (22) International Filing Date: 26 April 1996 (26.04.96) (30) Priority Data: 95810306.1 8 May 1995 (08.05.95) EP (34) <i>Countries for which the regional or international application was filed:</i> GB et al. (71) Applicant (for all designated States except US): CIBA-GEIGY AG [CH/CH]; Klybeckstrasse 141, CH-4002 Basle (CH). (71)(72) Applicant and Inventor: GURNY, Robert [CH/CH]; 7, rue Calvin, CH-1204 Geneva (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): ALLÉMANN, Eric, Olivier [CH/CH]; 253, route d'Annecy, CH-1257 Croix-de-Rozon (CH). LEROUX, Jean-Christopher [CA/CH]; 10, rue William-Favre, CH-1207 Geneva (CH). (74) Common Representative: CIBA-GEIGY AG; Patentabteilung, Klybeckstrasse 141, CH-4002 Basle (CH).		(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NANOPARTICLES FOR ORAL ADMINISTRATION OF PHARMACEUTICAL AGENTS OF LOW SOLUBILITY		
(57) Abstract The present invention relates to pharmaceutical compositions for the oral administration of pharmaceutical agents having low water solubility. Those agents are solubilized with a polymer suitable for the formation of nanoparticles, especially from the EUDRAGIT L and S series which release the active agent in specific target regions of the gastrointestinal tract.		

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Nanoparticles for Oral Administration of Pharmaceutical Agents of Low Solubility

The present invention relates to pharmaceutical compositions for the oral administration of pharmaceutical agents of low water-solubility and to a process for the preparation of said pharmaceutical compositions.

The oral administration of pharmaceutical agents formulated as tablets, capsules, or dragees has certain advantages over parenteral administration such as i.v. or i.m.. A certain psychological aspect cannot be ignored. Diseases requiring treatment with "painful" injectable formulations are considered far more "serious" than those diseases being treated with other oral dosage forms. The really important advantage of oral formulations is held to be their suitability for self-administration by the patient as against parenteral formulations that have to be administered in most cases by a physician or paramedical personnel.

An oral dosage form desaggregates after administration and is then subjected to the action of liquids present in the gastrointestinal tract, such as gastric and intestinal juices. A large group of orally administered active agents have lipophilic properties and are, therefore, sparingly soluble in those liquids. This diminishes the amount available for resorption which, in turn, reduces the bioavailability of the active agent administered. To compensate for such loss of bioavailability, the administration of a higher dose is required. However, higher doses of many active agents having low water solubility such as NSAIDs, e.g. acetylsalicylic acid or ibuprofen, or bisphosphonates, e. g. sodium pamidronate, are undesirable because of side-effects such as peptic ulceration.

Accordingly, the problem to which the present invention relates may be defined as follows: It is desirable to provide an oral dosage form for active agents of low water solubility in a physiologically acceptable dose. To solve this problem it is necessary to enhance the solubility of the active agent to be administered in the oral dosage form.

Numerous attempts have been made according to the prior art to increase the solubility of an active agent, especially in fluids present in the gastrointestinal tract (GIT). One approach is the addition of so-called solubility promoters or solubilizers, e.g. hydrophilic co-solvents such as ethanol or propylene glycol, liquid polyethylene glycols, or lipophilic

solubilizers such as lecithin, polyglycol esters of fatty acids or polyglycol esters of fatty acid glycerides. The use of those solubilizers generates other problems, for example diminished stability due to phase separation of the individual components of the formulation, or lower gastrointestinal tolerance. Many solubilizers are not acceptable for the incorporation in oral dosage forms.

If the addition of the above-mentioned solubilizers still fails to promote the solubility of the active agent, the incorporation in a homogenous lipid dispersion has been proposed. In such a dispersion the active agent is encapsulated in lipid particles having a particle size smaller than 1 μm . The "loaded" lipid particles then form with the aqueous carrier liquid an aqueous phase of colloidally dispersed or, preferably, finely dispersed character, which differs from the true homogeneous distribution of solutes at molecularly dispersed level but is, nevertheless, sufficiently homogeneous for the preparation of intravenous and oral dosage forms.

Numerous publications suggest the incorporation of active pharmaceutical agents of low solubility in micells, mixed micells, reversed micells, unilamellar or multilamellar liposomes, nanocapsules or nanoparticles.

These methods have the clear advantage of improved solubilization of an active agent having markedly low solubility. Unfortunately, these advantages are again diminished by other problems, including the low stability of the aqueous systems due to the separation of the phase into the individual components, insufficient amounts of encapsulated active agent, the strong dependency of the particle size on the method and conditions employed, unsatisfactory uniformity and insufficient reproducibility of the products obtained, and other problems.

Surprisingly, it has now been found that selected pharmaceutically acceptable polymers are suitable for the preparation of nanoparticles which encapsulate the active agent of low water-solubility in therapeutically effective amounts and release the active agent in target regions of the gastrointestinal tract.

The present invention relates to a pharmaceutical composition for the oral administration of an active agent having low water-solubility, wherein

- a) the active agent is dispersed in an aqueous formulation base; and
- b) the solubilizing agent is suitable for the formation of an aqueous dispersion of nano-particles;

which is characterized in that the solubilizing agent is a pharmaceutically acceptable polymer which is resistant to gastric juices and soluble in intestinal juices.

The pharmaceutical composition according to the present invention has the benefit of providing an enhanced solubility and bioavailability of the active agent to be administered in the oral dosage form. The active agent is released in selected target regions of the gastrointestinal tract such as the small intestine. The release in those regions is desirable in view of improved resorption through larger areas of the epithelium and of larger amounts of juice present in the intestine which reduces the risk of ulceration as compared with gastric resorption.

The general terms used throughout the specification of this invention are preferably defined as follows:

The term pharmaceutical composition means a mixture containing the active agent of low water-solubility to be administered in the oral dosage form to a host in a therapeutic method of treating the disease or condition indicated.

The term oral administration means the enteral administration of a dosage form commonly known as oral dosage form.

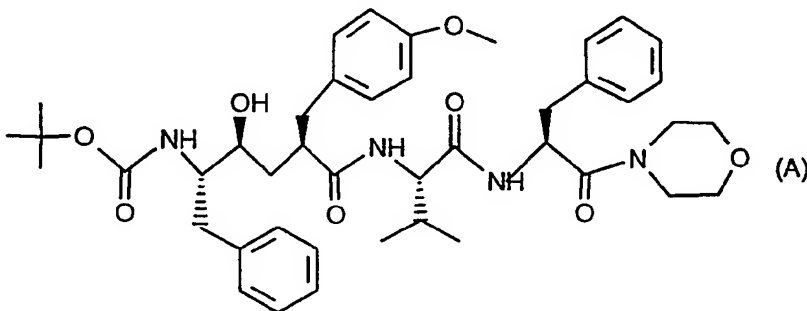
Oral dosage forms are in particular solid oral dosage forms containing defined amounts of the active agent, such as capsules or sachets, but also liquid dosage forms, such as droplets, suspensions, or emulsions. Capsules are dry-filled capsules made of gelatin, especially hard gelatin, which are prepared, where appropriate, with the addition of solid excipients, and which are dissolved without time delay by the action of gastric juice to release the components a) and b). Suitable excipients such as sorbitol, lactose, starch, or magnesium stearate, may be admixed. Soft capsules, may contain the liquid dosage forms mentioned, in particular suspensions or emulsions. They may contain, as additives, glycerol, lecithin, fats, oil, paraffin oil or liquid polyethylene glycol. Dry-filled capsule sizes 0-4,

preferably 0-2, are suitable, depending on the dose to be administered. Commercial products marketed by Eli Lilly, Elanco, Capsugel, Shionogi, or Scherer are suitable.

Sachets are containers, e.g. bags made of polyethylene, lined paper or aluminum foil, that contain components a) and b) and, optionally, additives such as lactose or starch. The composition may be removed directly after opening the sachet and administered orally, e.g. admixed with water.

An active agent of low water solubility preferably has a water solubility of less than 500 mg/1000 ml, particularly less than 200 mg/1000 ml and may be selected from any therapeutic group such as immune suppressive agents, non-steroidal antiinflammatory agents (NSAID), calcium channel blockers, immunomodulators, antibiotic agents and others.

A particularly preferred active agent having low water solubility is a selected HIV-1 protease inhibitor to which the following formula has been assigned:



HIV-1 protease was first suggested by Kramer et al. (Science **231**, 1580 - 1584, (1986)) being a target for AIDS treatment. Since then several types of HIV-1 protease inhibitors have become known. Like many other active agents of peptidic structure, this HIV-1 protease inhibitor (A) has a relatively short half-life in some in-vivo pharmaceutical models (mouse) and suffers from an insufficient oral bioavailability. The latter effect is presently attributed to the extremely low aqueous solubility (8 mg/ 1000 ml at pH 7.4).

The following nomenclature has been assigned to the HIV-1 protease inhibitor of the formula (A) given above:

Boc-Phe[C]-(p-CH₃O)Phe-(L)-(Phe-morpholin-4-yl)-amide or 5(S)-tert.-Butoxycarbonyl-amino-4(S)-hydroxy-2(R)-4-methoxyphenylmethyl-6-phenyl-hexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide. This compound is referred to in this specification as HIV-1 protease inhibitor of formula A or, where appropriate, as active agent. The preparation of this compound is described in the Published European Patent Application (EP-A) No. 618 222 (publication date Oct. 5, 1994).

The term "solubilized" means the homogenous dispersion of the active agent having low water solubility in an aqueous phase with the aid of a pharmaceutically acceptable solubilizer which is suitable for the preparation of nanoparticles.

Nanoparticles are solid spheroid particles ranging in size from about 10 to 1000 nm. When dispersed in an aqueous phase, they have colloidal properties. Nanoparticles is a generic term that comprises nanospheres and nanocapsules. Nanospheres have a polymeric matrix type structure, whereas nanocapsules have a shell formed of polymers surrounding an inner liquid core. Nanoparticles encapsulate the active agent of low water solubility.

The term "encapsulate" means the presence of an active agent having low water solubility in nanoparticles. In nanospheres, the active agent may be adsorbed at their surface, or entrapped, e. g. as microcrystals, in the polymeric matrix or dissolved therein. In nanocapsules the active agent may be dispersed in the liquid present in the inner core, but may also be adsorbed at the surface.

The term "aqueous formulation base" means the aqueous carrier liquid wherein the nanoparticles containing the active agent having low water solubility are homogeneously dispersed. The carrier liquid may contain conventional additives customarily used for preparing liquid oral dosage forms which are administered directly in the form of syrups or drops or administered with the aid of small containers such as capsules.

A solubilizing agent which is suitable for the formation of an aqueous dispersion of nanoparticles is, for example, a pharmaceutically acceptable copolymer which is resistant to gastric juice and soluble in intestinal juices. This copolymer inhibits the release of the active agent under strongly acidic conditions present in gastric fluids but allows the controlled

release of the active agent (drug targeting) from nanoparticles in pH-neutral or slightly basic juices present in the small intestine. The largest amount of active agent is released in the duodenum, but some release in the jejunum is also possible.

A suitable copolymer, which is resistant to gastric juice and soluble in intestinal juices, is formed from monomers selected from the group consisting of methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters. Those polymers are commercially available from Röhm Pharma GmbH, Weiterstadt Germany marketed under the trademark EUDRAGIT (Registered Trademark of Röhm Pharma GmbH).

An especially preferred polymer is the 1:1- up to 1:2-copolymer which is resistant to gastric juice and soluble in intestinal juices and which is formed from monomers selected from the group consisting of methacrylic acid and methacrylic acid lower alkyl esters, such as the 1:1- up to 1:2-copolymer from methacrylic acid and methyl methacrylate. The 1:1-copolymers are marketed in the EUDRAGIT L series. The corresponding 1:2-copolymers are marketed in the EUDRAGIT S series.

An especially preferred polymer is the 1:1-copolymer of methacrylic acid and acrylic acid ethyl ester. This polymer is marketed under the product name EUDRAGIT L 100-55.

An alternative polymer suitable for the formation of nanoparticles is polyvinyl acetate phthalate (PVAP) or a pharmaceutically acceptable cellulose derivative selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), and cellulose acetate trimellitate (CAT).

HPMCP is marketed as aqueous dispersion by Eastman Kodak Corp.. HPMCP 50 (USP/NF type 220824) and HPMCP 55 (USP/NF type 200731) are especially preferred.

CAP is marketed as aqueous dispersion under the trademark AQUATERIC (Registered Trademark of FMC Corp.) or is commercially available from Eastman (composition: phthalyl 35 %, acetyl 24 %, moisture 1 %, free acid 0.5 % (as phthalic acid)).

CAT is commercially available from Eastman (composition: trimellityl 29 %, acetyl 22 %, moisture 1 %, free acid 0.5 % (as phthalic acid)).

The present invention also relates process for the preparation of the pharmaceutical composition, which is characterized in that an aqueous dispersion of nanoparticles containing a) the active agent to be solubilized and b) the solubilizing agent, which is suitable for the formation of an aqueous dispersion of nanoparticles, is formed; and the dispersion is processed further under the optional addition of pharmaceutically acceptable additives c), which are suitable for the incorporation in a dosage form for the oral administration.

Various methods for carrying out this process are known. They are compiled in the publication of Eric Allémann et al., Eur. J. Pharm. Biopharm. 39(5), 173 - 191 (1993). The methods for the preparation of nanospheres are particularly preferred.

An especially preferred method comprises the preparation of an aqueous gel containing a hydrophilic polymer under the optional addition of a water soluble salt. This gel is then combined with a solution of a non-toxic organic solvent containing the active agent and the polymer which is suitable for the formation of an aqueous dispersion of nanoparticles. Phase separation is observed, and after addition of water the nanoparticles formed are homogeneously dispersed in the aqueous phase. The aqueous phase is then processed further to the pharmaceutical dosage form intended, e.g. by applying conventional purification and separation methods.

The preparation of the aqueous gel containing the hydrophilic polymer is disclosed in the reference of E. Allémann, loc. cit., and the references cited therein. The gel is formed by the addition of water to the hydrophilic polymer. Suitable hydrophilic polymers are polyvinyl alcohols, such as the ones marketed under the trademark MOWIOL (Registered Trademark of Hoechst AG, Germany). Preferred are polyvinyl alcohols having a degree of hydrolysis of more than 70 % (partially hydrolyzed grades), especially more than 87 %, e.g. MOWIOL from the 88 and 92 series, e.g. 4-88, 5-88, 8-88, 18-88, 23-88, 26-88, and 40-88. To facilitate the phase separation from the organic phase subsequently added, the addition of a physiologically acceptable water-soluble salt, such as magnesium chloride, or magnesium acetate, to the gel phase is preferred.

The gel phase is added under stirring to a solution of a non-toxic organic solvent, e.g. acetone or benzyl alcohol, containing the active agent, e.g. the HIV-1 protease inhibitor of the formula (A) of above, and the pharmaceutically acceptable polymer, which is suitable for the formation of nanoparticles defined above, especially EUDRAGIT from the L and S series, especially EUDRAGIT L 100, L 100-55 or S 100.

Pure water is added to allow the diffusion of the organic solvent to the aqueous phase, and the nanoparticles are formed and homogeneously dispersed therein. The aqueous phase may be processed further by conventional purification and separation methods resulting in the preparation of the dosage form desired.

The dispersion obtained may be defined as aqueous suspension of nanoparticles containing the active agent having low water-solubility. According to the preferred method of phase separation of the aqueous gel from the organic solvent, a homogeneous dispersion of nanospheres is obtained. Nanospheres are clearly distinguishable with physical methods, such as photon correlation spectroscopy (PCS), e. g. with a COULTER NANO-SIZER, LASER light scattering methods, or electron microscopy from other microparticles such as liquid crystals, micells, reversed micells, liposomes, microspheres or microcapsules. For a statistical average of more than 80 %, preferably more than 90 %, a mean average particle size between 60 and 300 nm has been determined. The size of the nanoparticles obtained depends on the established and known methods chosen for their preparation.

The homogenous dispersion containing nanospheres is then processed further to a conventional pharmaceutical dosage form by applying standard purification methods, such as the ones known in the art for purifying nanoparticles, such as ultracentrifugation, cross - flow filtration, or sterile filtration. The dispersion can also be lyophilized in a conventional manner and the lyophilisate is reconstituted to the pharmaceutical dosage form desired.

An oral dosage form is prepared by applying known methods such as the ones mentioned in Hagers Handbuch der Pharmazeutischen Praxis or Remington's Pharmaceutical Sciences. The additives customarily used for the preparation of oral dosage forms may be added if necessary. Their choice depends on the type of dosage form requested, e. g. solid or liquid oral dosage forms.

The homogeneous dispersion containing the nanospheres may also be converted to a lyophilisate which is reconstituted by the addition of water before the dispersion is administered. Even after reconstituting the lyophilisate, a homogenous nanodispersion is formed again. When preparing the lyophilisates, the addition of calculated amounts of water soluble additives is recommended.

The homogeneous dispersion, optionally after concentration to standardized volumes, or the lyophilisate is then added to suitable containers for unitary dosage forms, such as vials.

The following Examples are illustrating the invention as disclosed in the instant specification without limiting the scope thereof; temperatures are given in degrees Celsius; all percentages mentioned are weight percentages (w/w):

Example 1

1 a) An aqueous gel (42.5 g) containing 60 % magnesium chloride hexahydrate and 11 % polyvinyl alcohol (MOWIOL 4-88, Höchst) is added under stirring (1200 rpm) to an acetone solution (17 g) containing 16.2 % EUDRAGIT S 100 and 1.8 % HIV-1 protease inhibitor of formula A, resulting in the formation of an oil-in-water emulsion. Pure water (50 g) is added to allow the diffusion of acetone into the aqueous phase, with the result of forming monodispersed polymeric nanoparticles.

1 b) The nanoparticulate dispersion is then purified by cross-flow filtration using a SARTOCON Mini Device (Sartorius, Göttingen, Germany) mounted with a polyolefin cartridge filter with a 100 nm pore size. The filtration procedure is stopped after collecting 10 l of filtrate. The aqueous dispersion is finally frozen for 10 minutes at -55° and freeze-dried for 24 h at 0.05 mbar.

1 c) The lyophilisate is reconstituted in water with gentle agitation. The average particle size measured with a COULTER NANO-SIZER before purification with cross-flow filtration is 264 nm (polydispersity index: 2) and after reconstitution of the lyophilisate is 268 nm (polydispersity index: 3). The freeze-dried nanoparticles contain 9.8 % of the active agent.

Example 2

An aqueous gel (40 g) containing 14 % polyvinyl alcohol (MOWIOL 4-88, Höchst) is added under stirring (1200 rpm) to a benzyl alcohol solution (17 g) containing 12.8 % EUDRAGIT L 100 and 1.42 % active agent, resulting in the formation of an oil-in-water emulsion. Pure water (660 g) is added to allow the diffusion of benzyl alcohol into the aqueous phase, with the result of forming monodispersed polymeric nanoparticles.

The aqueous dispersion of nanoparticles is purified and freeze-dried for 46 h as described in Example 1 b). The lyophilisate is reconstituted in water with gentle agitation. The average particle size measured with a COULTER NANO-SIZER before purification with cross-flow filtration is 265 nm (polydispersity index: 2) and after reconstitution of the lyophilisate is 271 nm (polydispersity index: 1). The freeze-dried nanoparticles contain 10.0 % of the active agent.

Example 3

Nanoparticles are prepared, purified and freeze-dried as described above in Example 1a) and 1 b). EUDRAGIT S 100 is replaced with EUDRAGIT L 100-55. The lyophilisate is reconstituted in water with gentle agitation. The average particle size measured with a COULTER NANO-SIZER before purification with cross-flow filtration is 240 nm (polydispersity index: 2) and after reconstitution of the lyophilisate is 246 (polydispersity index: 2). The freeze-dried nanoparticles contain 9.6% of the active agent.

Claims:

1. A pharmaceutical composition for the oral administration of an active agent having low water solubility, wherein
 - a) the active agent is dispersed in an aqueous formulation base; and
 - b) the solubilizing agent is suitable for the formation of an aqueous dispersion of nano-particles;which is characterized in that the solubilizing agent is a pharmaceutically acceptable polymer which is resistant to gastric juices and soluble in intestinal juices.
2. A pharmaceutical composition according to claim 1, wherein the polymer, which is resistant to gastric juices and soluble in intestinal juices is a copolymer from monomers selected from the group consisting of methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters.
3. A pharmaceutical composition according to claim 1, wherein the polymer, which is resistant to gastric juices and soluble in intestinal juices is a pharmaceutically acceptable cellulose derivative selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose-phthalate (HPMCP), celluloseacetate-phthalate (CAP), and celluloseacetatetrimellitate (CAT).
4. A pharmaceutical composition according to claim 2, wherein the polymer is a 1:1- up to 1:2-copolymer from monomers selected from the group consisting of methacrylic acid and methacrylic acid lower alkyl esters.
5. A pharmaceutical composition according to claim 4, wherein the copolymer is a 1:1- up to 1:2-copolymer of methacrylic acid and methacrylic acid methyl ester.
6. A pharmaceutical composition according to claim 2, wherein the copolymer is a 1:1-copolymer of methacrylic acid and acrylic acid ethyl ester.
7. A pharmaceutical composition according to claim 1, wherein the solubilizing agent is suitable for the formation of nanospheres.

8. A pharmaceutical composition according to claim 1, wherein the formulation base contains water soluble additives suitable for incorporation in a dosage form intended for oral administration.

9. A process for the preparation of the pharmaceutical composition according to claim 1, which is characterized in that an aqueous dispersion of nanoparticles containing a) the active agent to be solubilized and b) the solubilizing agent, which is suitable for the formation of an aqueous dispersion of nanoparticles, is formed; and the dispersion is processed further under the optional addition of pharmaceutically acceptable additives c), which are suitable for the incorporation in a dosage form for the oral administration.

10. A process according to claim 9, characterized in that the aqueous dispersion of nanoparticles is processed further to a lyophilisate.

11. A process according to claim 9, characterized in that the aqueous dispersion of nanoparticles is filled into starch, hard gelatin or soft gelatin capsules.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/EP 96/01769

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MICROENCAPSULATION, vol. 8, no. 2, April 1991 - June 1991, GB, pages 161-170, XP000216615 R. BODMEIER ET AL: "Spontaneous formation of drug-containing acrylic nanoparticles"	1,2,4-10
Y	see abstract see page 163, line 38 - line 47 see page 164, last paragraph - page 165, line 8	3
Y	--- US,A,5 382 435 (R. S. GEARY ET AL) 17 January 1995 see the whole document	3
A	--- EP,A,0 275 796 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE) 27 July 1988 see claims 1-15 see page 3, column 3, line 33 - line 46 --- -/-	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

11 September 1996

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PCT/EP 96/01769

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,2 166 651 (ELAN CORP.) 14 May 1986 see claims 1-15 see page 3, line 30 - line 39 ---	1-11
A	EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 39, no. 5, October 1993, DE, pages 173-191, XP000403429 E. ALLEMANN ET AL: "Drug-Loaded Nanoparticles - Preparation Methods and Drug Targeting Issues" cited in the application see page 177, right-hand column, line 1 - page 179, right-hand column, line 19 see page 182, left-hand column, line 42 - right-hand column, line 36 -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No

PCT/EP 96/01769

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